

Applicants also respectfully request the opportunity to supplement the present response in light of any agreements reached during the October 7, 2003 interview, before the Examiner takes further action in this matter.

REMARKS

No further amendments are presented. Claims 1-13, and 38-41 remain pending in the application.

Enclosed is a check for \$410 for a two-month extension of time, to extend the time for response from July 2, 2003 to September 2, 2003. (37 C.F.R. § 1.136(a)(3)). If this amount is incorrect, please refer to the Deposit Account Authorization previously filed for this application. If any additional extension of time is required, please consider this paper a petition for the total extension of time required.

Reexamination and reconsideration of the application are respectfully requested.

The Claim Objection

Claim 1 was objected to as containing an apparent typographical error, such as the use of a comma before the "and" in line 8. It is respectfully submitted that it is preferred usage to include a comma before a conjunction such as "and" in a series of three or more terms. The Office is referred, for example to page 2, rule 2 of Strunk and White, *The Elements of Style* (Third Edition 1979).

It is respectfully submitted that this ground of objection should be withdrawn.

The § 112, Second Paragraph Rejections

Claims 1-13, and 38-41 were rejected under 35 U.S.C. § 112, second paragraph on several grounds. The Office gave specific grounds of rejection only for Claims 1, 2, and 40, so it is assumed that the remaining Claims were rejected solely due to their dependence from independent Claim 1 or dependent Claim 40.

Claim 1

Claim 1 was said to be indefinite in the phrases “other cells of the tissue” and “including blood vessels, supportive stromal elements, neural cells, and endothelial cells.” This ground of rejection is not fully understood. Applicants suggest that this ground of rejection be clarified and further discussed at the upcoming personal interview.

Claim 1 was also said to be indefinite in the phrase “if any.” Some tissue samples will exhibit angiogenesis, while other tissue samples will exhibit no angiogenesis. In the latter case, no angiogenic vessels will be observed. An observation that there is no angiogenesis associated with a particular sample can provide useful and valuable information. Therefore it is appropriate and accurate for the Claim to refer to “angiogenic vessels, if any.”

The Office also said that the limitation “time sufficient” was indefinite. It is respectfully submitted that not only is the limitation in question definite, but that it highlights the need for the phrase “if any” to which the Office also objected. The full limitation in question is incubating “for a time sufficient to allow angiogenic vessels, if any, to grow into the matrix” A person of ordinary skill in the art would readily understand this limitation to mean that the time is sufficient for angiogenic vessels to grow into the matrix --

assuming that there are angiogenic vessels -- and otherwise, that the time is sufficient to demonstrate the fact that there are none, because angiogenic vessels would have grown into the matrix within the allotted "sufficient" time, had such vessels been present.

The Office's attention is respectfully directed to M.P.E.P. § 2173.05(g), "Functional Limitations": "A functional limitation is an attempt to define something by what it does, rather than by what it is There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. . . . A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient, or step." (citations omitted)

A person of ordinary skill in the art, given the teachings of the present specification, could readily determine and understand what constitutes "a time sufficient to allow angiogenic vessels, if any, to grow into the matrix . . ." for a particular set of conditions.

In reply to a similar argument made in the Applicants' prior response, the Office asserted that either the definition of "angiogenic vessels" or the presence of "angiogenic vessels" was uncertain. With all respect, a person of ordinary skill in the art would readily understand what is meant by "angiogenic vessels," and would readily comprehend what is meant by whether "angiogenic vessels" are present. A person of ordinary skill in the art would readily understand these concepts even in the absence of the teachings of the present specification. But hypothetically, if there were any question as to what "angiogenic vessels" are, there is discussion throughout the present specification, including, for

example, at page 1, lines 22 through 29; page 15, line 27 through page 16, line 5; and page 17, lines 22-28.

Functional language is permissible, and in many instances is a preferred manner to define an invention. The use of functional language in Claim 1 introduces no indefiniteness; a person of ordinary skill in the art would readily understand the claim limitations as currently written. It is respectfully submitted that this ground of rejection should be withdrawn.

Claim 2

Claim 2 was said to be indefinite in its use of the word "substantially." The Office has recognized that the M.P.E.P. acknowledges that the use of the term "substantially" is often definite, depending on context. See M.P.E.P. § 2173.05(b), subheading D. The Office asserted, however, that the term was nevertheless indefinite because neither the specification nor the Claims gave particular definitions of amounts that were included or excluded by the term "substantially."

It is respectfully submitted that the Office is mistaken in asserting that the term "substantially" must find specific metes and bounds in the specification or in the claims before the term may be considered definite. M.P.E.P. § 2173.05(b), subheading D gives two examples in which the term substantially has been found by the Courts to be definite: in one example, the specification did provide general guidelines; but in the second example, the Court found the term definite because "one of ordinary skill in the art would know what was meant by 'substantially equal.'" (citations omitted)

In the context of Claim 2, the term “substantially” is definite. A person of ordinary skill in the art would readily understand the meaning of the term in context, and § 112, second paragraph is therefore satisfied. There is no requirement for mathematically precise metes and bounds if, as in the present case, a person of ordinary skill in the art would readily understand the meaning of the limitation in question.

The full expression appearing in Claim 2 is “wherein the medium contains substantially no exogenous angiogenesis-enhancing factors and substantially no exogenous angiogenesis-suppressing factors.” In other words, it is not necessary to exclude every last molecule of any enhancing or suppressing factors. The limitation is, of course, consistent with the complete absence of enhancing or suppressing factors. But a person of ordinary skill in the art would readily understand that the limitation is also consistent with the possible presence of small quantities of enhancing factors, or small quantities of suppressing factors, or both. However, if such a factor is present, then its concentration should be such that the observed angiogenesis of tissue samples in the medium is substantially the same, on average, as would be observed in an otherwise identical medium that completely lacked the factor. If the observed average angiogenesis were substantially different from that in an otherwise identical medium that completely lacked the factor, then the medium would not be considered to be substantially free of the factor. A person of ordinary skill in the art would readily comprehend the meaning of these limitations. The Claim limitations in question are definite.

Claim 40

Claim 40 was said to be indefinite on three different grounds. One of these grounds refers to a typographical error that may readily be corrected, namely the double inclusion of "pancreatic tissue" in the Markush group.

However, it is not understood why the Office has asserted that two other limitations of the Markush group were said to be unclear -- namely, "tissue from a wound," and "a transplanted tissue." These terms would be readily understood by a person of ordinary skill in the art.

Applicants suggest that these last two grounds of rejection be clarified and further discussed at the upcoming personal interview. Following the interview, an appropriate amendment to Claim 40 will be drafted and filed -- including both correction of the typographical error regarding "pancreatic tissue," and such other amendments, if any, as may be agreed at the interview.

§ 112, Second Paragraph Summary

It is respectfully submitted that all § 112, second paragraph rejections have been overcome or should be withdrawn. Applicants suggest that certain grounds of rejection be clarified and further discussed at the upcoming personal interview.

The §§ 102 and 103 Rejections

All Claims were rejected under 35 U.S.C. §§ 102(b) and 103 as being both anticipated by, and obvious over, one or more of four different references cited by the Office.

It is respectfully submitted that the claimed inventions are both novel and nonobvious over the cited references, whether those references are considered individually or in combination.

Claim 1 is the sole independent Claim within this Group of Claims. Without waiving the right to assert alternative arguments in the future, in the interest of brevity Applicants will discuss only Claim 1 for the time being. If independent Claim 1 is novel and nonobvious, then it logically follows that the dependent Claims must also be novel and nonobvious. Further in the interest of brevity, for the time being only a single reason will be argued why Claim 1 is distinguishable from the cited references, since that reason is particularly straightforward.

The “three-dimensional tissue sample” and “substantially intact” architecture limitations

Independent Claim 1 contains the following limitation that is neither taught nor suggested by any of the cited references:

“embedding a three-dimensional mammalian tissue sample in
a matrix”

Claim 1 also clarifies what this limitation means:

“wherein the three-dimensional tissue sample comprises multiple layers of cells comprising blood vessels and other cells of the tissue; and wherein the

architecture of the tissue sample, including blood vessels, supportive stromal elements, neural cells, and endothelial cells, is substantially intact and has not been disrupted as compared to that of comparable tissue *in vivo*”

Some of the advantages of the novel system over the prior references are explained in the specification at page 15, lines 1-20, and page 21, lines 1 through 24:

No prior reports are known of angiogenesis assays for tumors or other tissue in which the intact three-dimensional structure of the tissue is maintained during the assay -- as opposed to, for example, reports of an assay conducted on an isolated artery or vein. . . .

We have discovered an *in vitro* tissue angiogenesis and vasculogenesis system that allows the outgrowth of microvessels from a three-dimensional tissue fragment implanted in a matrix. . . . This system, which may be used with human or other mammalian or animal tissues, may be used in assaying tumor angiogenic potential The angiogenic potential of a tissue can be determined by measuring the growth of microvessels into the matrix. The system is based on endogenous angiogenesis, vasculogenesis, neovascularization, or tissue perfusion, independent of tumor angiogenesis or other tissue angiogenesis. By contrast, tumor angiogenesis *per se* results from the formation of patterned

networks of interconnected loops of extracellular matrix through which tumor perfusion may occur. The three-dimensional structure of the tumor or other tissue is maintained in the matrix, including its blood vessels, supportive stromal elements such as fibroblasts, and neural and endothelial cells. . . .

The invention allows a tumor or other tissue to induce an angiogenic response while maintaining an intact three-dimensional architecture.

The present invention offers several advantages. It allows the evaluation of a tumor or other tissue's angiogenic response while maintaining an intact three-dimensional architecture. Tumor (or other tissue) compartments may be evaluated simultaneously or separately. The novel system allows the evaluation of drugs that require activation *in vivo* and drugs that are active *ex vivo*. One advantage of this invention is that it may be used to provide a functional (as opposed to histological) angiogenic index. A functional angiogenic index may help to reveal tumors with a poor prognosis due to a high functional angiogenic index, even though they may have a low histological angiogenic index. A disparity between functional and histological angiogenic indices may occur if circulating anti-angiogenic substances (such as angiostatin/endostatin) mask the angiogenic potential of a tumor. . . .

The invention may also be used to develop prognostic tests for a patient's resistance or susceptibility to the future development of malignancy or angiogenesis-related diseases.

With this background, a straightforward examination of the cited references readily reveals that none of them teaches or suggests the use of a "three-dimensional" tissue sample having a "substantially intact architecture" within the scope of the definition of Claim 1.

Brown

The source of the vessel fragments is given on page 550, col. 1, under the heading "Preparation of blood vessel fragments." Superficial blood vessels were excised from the surface of human placentas, cut into 1- to 2-mm fragments, and freed of residual clots. For the reasons just discussed, fragments of an isolated blood vessel are outside the definition found in Claim 1.

The April 2, 2003 Office Action at page 8 speculated that other cell types were present along with the blood vessels excised in Brown, but Brown gives no reason to believe that this should have been the case. To the contrary, Brown refers to excising "superficial" blood vessels, i.e., blood vessels readily removed at the surface of the placenta, and to freeing those blood vessels of residual clots. Brown gives no reason to believe that other cell types were present. But more significantly, even if one assumed for the sake of argument that other cell types were indeed present, they would presumably have only been present on the surface of the excised blood vessels only in small numbers.

And they certainly would not -- as required by Claim 1 -- have preserved a "substantially intact" three-dimensional architecture as compared to that of comparable tissue *in vivo*.

Montesano

The Office cited the abstract, page 807 (it is assumed that "page 870" was intended) at the "Materials and Methods" section, and figures 1 and 2. Montesano's abstract does include the words "three-dimensional." However, there is no indication of any sort that Montesano had the present definition of "three-dimensional" in mind. Furthermore, Montesano's reference to a particular "three-dimensional" element was in fact a reference to a three-dimensional matrix, not a three-dimensional tissue sample. See the first two lines of Montesano's abstract. The samples used were described in the first paragraph of the "Materials and Methods" section on page 870. Tissues (from various sources) "were minced into small fragments in a drop" of saline. One may therefore reasonably infer that the individual tissue fragments must have been considerably smaller than the size of a drop of saline. In the following paragraph, there is a further indication of the size of the "small fragments" where it is stated that the "tissue fragments were . . . allowed to sediment, and resuspended" in solution. The fragments must indeed have been small if it was necessary to allow them to sediment, and if they could be said to later be "resuspended." As stated in the examples following the detailed Definition found in the present specification, isolated cells from a disrupted tissue are not "three-dimensional" within the scope of the definition of Claim 1; nor is an agglomeration of such cells grown in culture -- even if the agglomeration has substantial thickness. See the present specification at page 29, lines 5-10.

The definition in Claim 1 requires that the architecture of the tissue sample be substantially intact, and not be disrupted as compared to that of comparable tissue *in vivo*. While there is no minimum size *per se*, the disruption and suspension of cells described by Montesano leads one to the reasonable deduction that the size of the samples must necessarily have been so small that they could not have maintained any intact architecture. The definition of Claim 1 refers to a substantially intact tissue architecture. When a sample has been disrupted to a sufficiently small size, as was done in Montesano, then it will be a necessary consequence that the tissue architecture must have been disrupted in the process. Conversely, if the cells are then allowed to grow into an agglomeration in culture, even if that agglomeration becomes relatively thick, the agglomeration would not satisfy the “substantially intact” architecture limitation of Claim 1. See the present specification at page 29, lines 5-10. The April 2, 2003 Office Action did not rebut these common-sense inferences.

Lugassy

To date, Applicants have not obtained a translation of this reference. For the time being, therefore, these remarks are based the “Abridged English Version” on pp. 37-38. This reference does mention a “three-dimensional” element, but again, there is no indication that Lugassy taught or suggested the use of a “three-dimensional” tissue sample having “multiple layers of cells comprising blood vessels and other cells of the tissue; and wherein the architecture of the tissue sample, including blood vessels, supportive stromal elements, neural cells, and endothelial cells, is substantially intact and has not been disrupted as compared to that of comparable tissue *in vivo*.”

To the contrary, the manner in which Lugassy's tumor model was prepared shows clearly that it was not a "three-dimensional" tissue sample with "substantially intact" architecture as required by the limitations of Claim 1. Lugassy teaches away from the present invention. Rather than use a "three-dimensional" tissue sample with substantially intact architecture, Lugassy teaches the use of a "rebuilt" tumor model, in which cells from a lymphoma cell line were mixed with angioma fibroblasts obtained by culturing explants from a human vascular angioma. The mixed cells were suspended in a collagen gel, which then grew into the "rebuilt" cancer. Cells from the "rebuilt" cancer became confluent in 4-8 weeks. This last statement implies that the cells were not confluent at an earlier time, i.e., that they were separated from one another. As previously discussed, isolated cells do not have the substantially intact architecture required by the limitations of Claim 1, nor does an agglomeration of such cells grown in culture -- even if the agglomeration grows to substantial thickness. See the present specification at page 29, lines 5-10.

With all respect, the Office is incorrect in asserting that applicants are relying on limitations not in the claims. The agglomerations reported in Lugassy do not have the "substantially intact" architecture required by Claim 1, and nothing in the Office's remarks suggests otherwise. Instead, the Office's remarks appear to overlook the "substantially intact" architecture limitation of Claim 1.

U.S. Patent 5,976,782

U.S. Patent 5,976,782 discloses methods for determining angiogenesis by culturing a blood vessel fragment in a physiological gel, such as fibrin, collagen, or Matrigel. This patent taught that "[p]referably, the blood vessel fragments are freshly isolated." Col. 3,

lines 57-58. The working examples (e.g., Col. 7, lines 44-57) describe the preparation of what appear to be isolated blood vessel fragments, cut into 1-2 mm fragments with fine dissecting forceps and iridectomy scissors, and freed of residual clots. There was no suggestion that any cell layers were retained, other than those of the blood vessel fragments themselves. See also Col. 8, lines 40-48, which describes occasional contamination of cultures by fibroblasts, ways to inhibit fibroblast outgrowth, and the observation that the fibroblasts appeared only as a monolayer on the bottom of culture wells, unable to penetrate the fibrin gels. These isolated blood vessel fragments fall outside the clear limitations of Claim 1, which expressly exclude “an isolated artery or an isolated vein.”

Contrary to the Office’s assertion that the samples in the ’782 patent included other cell types such as fibroblasts, the teachings of that patent teach away from the claimed inventions in treating occasional fibroblast contamination as something to be avoided, and in teaching ways to inhibit fibroblast contamination. Furthermore, since any fibroblasts were only monolayers on the bottom of wells, they lacked the “substantially intact” three-dimensional architecture required by independent Claim 1.

§§ 102 and 103 Summary

It is respectfully submitted that all prior art rejections should be withdrawn.

Compliance with 37 C.F.R. § 1.111(b) Regarding § 103 Rejections

Applicants interpret the Office’s remarks on page 18 of the April 2, 2003 Office Action as withdrawing the prior objection under 37 CFR 1.111(b).

The Information Disclosure Citations

The Office has again declined to consider the properly submitted Gulec *et al.* manuscripts. The record will be clear that Applicants have fulfilled any duty of disclosure that may exist with respect to these manuscripts, and that the manuscripts are available to the public as part of the file wrapper of the present application.

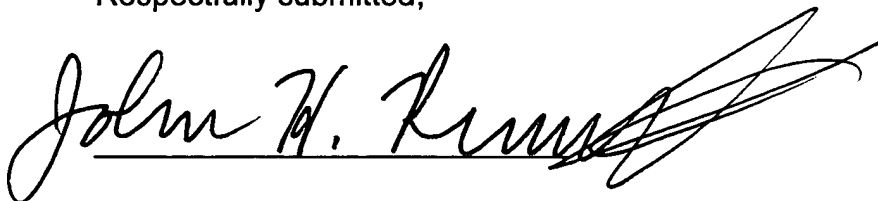
The Office is again reminded that neither 37 C.F.R. § 1.97 nor § 1.98 requires that a cited document be publicly available. To the contrary, 37 C.F.R. § 1.98(a)(1) refers to “patents, publications, applications, or other information.” “Other information” must be something that is not a publication, or the reference to “other information” would be superfluous. See also 37 C.F.R. § 1.98(2)(ii), which requires a legible copy of each publication, and § 1.98 (2)(iv), which requires a legible copy of “[a]ll other information.” By contrast, 37 C.F.R. § 1.99, which governs third-party submissions in published applications, allows third parties to submit copies of “patents or publications” in § 1.99(a), while § 1.99(d) expressly prohibits third-party submission of “other information.” Thus the Rules of the PTO clearly contemplate that patent applicants may submit “other information” that is neither a patent, nor a publication, nor an application; while third parties are limited to submitting patents and publications only.

While Applicants respectfully submit that the Office’s position is mistaken and should be reconsidered, Applicants will not continue to argue this point further.

Conclusion

Allowance of Claims 1-13, and 38-41 at an early date is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "John H. Runnels", with a horizontal line drawn underneath it.

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